

**Amendments to the Claims:**

This listing of the claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1 (Currently Amended). A method ~~of treating a tumor, having malignant cells, in a subject, comprising administering to said subject an amount effective to treat the tumor of a composition comprising~~in accordance with claim 27, wherein said agents comprise:

(A) an agent that causes a ~~decreases~~ decrease in the  $[GSH]^2/[GSSG]$  (wherein [GSH] is the concentration of glutathione and [GSSG] is the concentration of glutathione disulfide) ratio in the malignant cells of said tumor, selected from the group consisting of

(i) an agent that ~~oxidizes~~ causes oxidation of GSH, ~~or a precursor of said agent;~~ and

(ii) an agent that ~~forms~~ causes formation of an adduct or a conjugate with GSH, ~~or a precursor of said agent;~~ and

(B) an agent that ~~maintains~~ causes the decreased  $[GSH]^2/[GSSG]$  ratio to be maintained in the malignant cells of said tumor, selected from the group consisting of

(iii) an agent that ~~inhibits~~ causes inhibition of the GCS ( $\gamma$ -glutamylcysteine synthetase) enzyme, ~~or a precursor of said agent;~~

(iv) an agent that ~~inhibits~~ causes inhibition of the glutathione reductase (GR) enzyme, ~~or a precursor of said agent;~~ and

(v) an agent that ~~diminishes~~ causes the precursor of GSH to be diminished, ~~or a precursor of said agent,~~

wherein said agents are administered in amounts and in a manner such that a decreased  $[GSH]^2/[GSSG]$  ratio is reached and is maintained in the malignant cells continuously for about 15 to about 75 hours.

2-3 (Cancelled).

4 (Previously Presented). A method according to claim 1, wherein said agents are administered together with a standard chemotherapeutic drug.

5-6 (Cancelled).

7 (Previously Presented). A method according to claim 1, wherein

said agent of (i) is selected from the group consisting of disulfiram, hydrogen peroxide, a precursor thereof selected from the group consisting of ascorbic acid and dopamine,  $\alpha$ -lipoic acid, oxidized low density lipoproteins

(ox-LDLs), and a quinone selected from the group consisting of duroquinone, an ubiquinone, and  $\beta$ -lapachone, and

said agent of (ii) is selected from the group consisting of a Michael acceptor or another conjugating agent;

said agent of (iii) is buthionine sulfoximine (BSO);  
and

said agent of (iv) is carmustine.

8 (Previously Presented). A method according to claim 21, wherein said isoflavone is selected from the group consisting of catechin, daidzein, dicumarol, (-)epicatechin, flavopiridol, genistein,  $\beta$ -lapachone, myricetin and rotenone; said unsubstituted or partially substituted quinone is selected from the group consisting of anthraquinone, benzoquinone, 2-methylbenzoquinone, 2,6-dimethyl-benzoquinone, 2,5-dimethyl- benzoquinone, 2,3,5-trimethyl-benzoquinone,  $\gamma$ -tocopherolquinone and  $\delta$ -tocopherolquinone; said  $\alpha,\beta$ -unsaturated aldehyde is selected from the group consisting of cinnamaldehyde and a 4-hydroxy-C<sub>5</sub>-C<sub>9</sub>-alkenal selected from the group consisting of 4-hydroxy-C<sub>5</sub>-C<sub>9</sub>-pentenal, 4-hydroxy-C<sub>5</sub>-C<sub>9</sub>-hexenal, 4-hydroxy-C<sub>5</sub>-C<sub>9</sub>-heptenal, and 4-hydroxy-C<sub>5</sub>-C<sub>9</sub>-nonenal; and said phenol is selected from the group consisting of curcumin, (-)epigallocatechin-3-gallate, resveratrol,  $\gamma$ -tocopherol,  $\delta$ -tocopherol, yakuchinone A, and yakuchinone B.

9 (Cancelled).

10 (Previously Presented). A method according to claim 1, wherein said composition comprises at least one agent of (i) and at least one agent of (iii).

11 (Previously Presented). A method according to claim 10, wherein said at least one agent of (i) is disulfiram, hydrogen peroxide, a precursor thereof selected from the group consisting of ascorbic acid and dopamine,  $\alpha$ -lipoic acid, oxidized low density lipoproteins (ox-LDLs), and a quinone selected from the group consisting of duroquinone, an ubiquinone, and  $\beta$ -lapachone, and said at least one agent of (iii) is buthionine sulfoximine (BSO).

12 (Previously Presented). A method according to claim 1, wherein said composition comprises at least one agent of (i) and at least one agent of (iv).

13 (Previously Presented). A method according to claim 12, wherein said at least one agent of (i) is disulfiram, hydrogen peroxide, a precursor thereof selected from the group consisting of ascorbic acid and dopamine,  $\alpha$ -lipoic acid, oxidized low density lipoproteins (ox-LDLs), and a quinone selected from the group consisting of duroquinone,

an ubiquinone, and  $\beta$ -lapachone, and said at least one agent of (iv) is carmustine.

14 (Previously Presented). A method according to claim 1, wherein said composition comprises at least one agent of (ii) and at least one agent of (iii).

15 (Previously Presented). A method according to claim 1, wherein said composition comprises at least one agent of (ii) and at least one agent of (iv).

16 (Previously Presented). A method according to claim 1, wherein said composition is administered continuously to said patient for about 15 to about 75 hours.

17 (Previously Presented). A method according to claim 1, wherein said  $[GSH]^2/[GSSG]$  ratio that is maintained continuously for about 15 to about 75 hours is decreased in an amount such that E is increased by at least 10 mV during said period, wherein  $E = E_0 - 30 \log [GSH]^2/[GSSG]$ , and wherein  $E_0$  is the standard potential of glutathione.

18 (Previously Presented). A method according to claim 1, wherein said  $[GSH]^2/[GSSG]$  ratio that is maintained continuously for about 15 to about 75 hours is decreased in an amount such that E is increased above  $E_{CCP}$  during said period, wherein  $E = E_0 - 30 \log [GSH]^2/[GSSG]$ , wherein  $E_0$  is the

standard potential of glutathione, and wherein  $E_{CCP}$  is the redox potential where cessation of cell proliferation occurs.

19 (Previously Presented). A method according to claim 18, wherein E is increased to above about -200 mV during said period.

20 (Previously Presented). A method according to claim 19, wherein E is increased to between about -200 mV and -190mV during said period.

21 (Previously Presented). A method according to claim 7, wherein said Michael acceptor or other conjugating agent is selected from the group consisting of arsenic trioxide; diethylmaleate; ethacrynic acid; epothilone A or B; an  $\alpha,\beta$ -unsaturated aldehyde or ketone; a polyunsaturated fatty acid (PUFA); an unsubstituted or partially substituted quinone; an isoflavone; and a phenol.

22 (Previously Presented). A method according to claim 11, wherein said at least one agent of (i) is disulfiram and said at least one agent of (iii) is buthionine sulfoximine (BSO).

23 (Previously Presented). A method according to claim 12, wherein said at least one agent of (i) is disulfiram and said at least one agent of (iv) is carmustine.

24 (Previously Presented). A method according to claim 1, comprising at least one agent of (i), at least one agent of (iii) and at least one agent of (iv).

25 (Previously Presented). A method according to claim 24, wherein said at least one agent of (i) is disulfiram, said at least one agent of (iii) is buthionine sulfoximine (BSO) and said at least one agent of (iv) is carmustine.

26(New). A method of treating a tumor having an operative protein retinoblastoma (RB) protein, having malignant cells, in a subject, comprising administering to said subject a composition comprising an agent that causes a decrease in the  $[GSH]^2/[GSSG]$  (wherein  $[GSH]$  is the concentration of glutathione and  $[GSSG]$  is the concentration of glutathione disulfide) ratio in the malignant cells of said tumor, the amounts of said composition and the mode of said administration being such that a decreased  $[GSH]^2/[GSSG]$  ratio is reached and maintained in the malignant cells continuously for about 15 to about 75 hours.

27 (New). A method in accordance with claim 26, wherein said administering step comprises administering a synergistic combination of at least two agents, which combination causes a decrease in the  $[GSH]^2/[GSSG]$  ratio in the

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malignant cells of said tumor, wherein said agents are  
selected from the classes consisting of:

- (i) an agent that causes oxidation of GSH;
- (ii) an agent that causes formation of an adduct or  
a conjugate with GSH;
- (iii) an agent that causes inhibition of the GCS ( $\gamma$ -  
glutamylcystein synthetase) enzyme; and
- (iv) an agent that causes inhibition of the  
glutathione reductase (GR) enzyme.